10/

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/780,668	02/09/2001	Stephen D. Gillies	LEX-011	8264

21323 7590 03/09/2004

TESTA, HURWITZ & THIBEAULT, LLP
HIGH STREET TOWER
125 HIGH STREET
BOSTON, MA 02110

EXAMINER	
SAUNDERS, DAVID A	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 03/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
780,668	GILLIES et al
Examiner	**Group Art Unit**
SAUNDERS	1644

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☑ Responsive to communication(s) filed on 10/23/03.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 1 1; 453 O.G. 213.

Disposition of Claims

☑ Claim(s) 1-2, 4-8, 11-19, 24-25, 29, 34-37, 46-55 is/are pending in the application.

Of the above claim(s)_____ is/are withdrawn from consideration.

☐ Claim(s)_____ is/are allowed.

☑ Claim(s) 1-2, 4-8, 11-19, 24-26, 29, 34-37, 46-55 is/are rejected.

☐ Claim(s)_____ is/are objected to.

☐ Claim(s)_____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on_____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on_____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number)_____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received:_____.

Attachment(s)

☑ Information Disclosure Statement(s), PTO-1449, Paper No(s)._____

☐ Interview Summary, PTO-413

☑ Notice of Reference(s) Cited, PTO-892

☐ Notice of Informal Patent Application, PTO-152

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Other_____

Office Action Summary

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/23/03 has been entered.

Claims 1-2, 4-8, 11-19, 24-25, 29, 34-37 and 46-55 are pending and under examination.

The amendment has overcome previously stated issues as follows:

The objection to claim 47 under 37 CFR 1.75.

The rejection of claim 29 under 35 USC 112, 2nd paragraph.

The rejection of claims 1-2, 4-8, 11-19, 24-25, 29 and 34-37 under 35 USC 112, 1st paragraph.

Claims 1-2, 4-8, 11-19, 24-25, 29, 34-37 and 46-55 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In each of claims 1, 29, 48-49 and 51 "alteration to a hydrophobic or non-polar amino acid" can be interpreted two ways: 1) a hydrophobic or non-polar amino acid residue within the unaltered fusion protein is altered in some way (e.g. a charge group is added, as in an ala to asp change), and 2) an amino acid residue within the unaltered fusion protein is altered to be more hydrophobic or more non-polar (e.g. a charged group is removed, as in an asp to ala change). The disclosure supports only the second interpretation.

In claim 11 "said portion of heavy chain" lacks antecedent basis, because base claim 7 has recited "part of an Ig heavy chain" and not "portion" thereof.

Claim 29 is unclear as to where, in the Ig chain, and for what purpose the further amino acid alteration takes place. Is this further alteration also for the purpose of increasing circulating half-life, or for altering some other function – e.g. ADCC, FcRp binding, C' activation, etc.?

In claim 37 "said C-terminal residue" lacks antecedent basis, since "residue" has not been previously recited in any base claim. Also, one cannot tel whether the "non-lysine amino acid" is that before or after alteration. If the latter, then claim 37 does not limit claim 36, because "non-lysine" is broader than "non-ionizable".

In claim 53 it is not clear whether "the C-terminal amino acid" is the amino acid residue before or after alteration: one needs to further read dependent claim 54 to understand what is intended. Applicant should render claim 53 such that it clearly claims the antibody based fusion protein after alteration -- i.e. what the claimed antibody based fusion is, not what it was before alteration.

Claims 1-2, 4-8, 11-19, 24-25, 29, 34-37 and 46-55 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims contain new matter.

As noted supra, in each of claims 1, 29, 48-49 and 51 "alteration to a hydrophobic or non-polar amino acid" can be interpreted two ways. The disclosure supports only the second interpretation. The first interpretation introduces new matter.

Also, it was noted supra that Claim 29 is unclear as to where, in the Ig chain, and for what purpose the further amino acid alteration takes place. The examiner finds no disclosure of

altering any amino acid to be more hydrophobic or non-polar except for the purpose of increasing circulating half-life. If one reads this further alteration to be for the purpose of altering some other function — e.g. ADCC, FcRp binding, C' activation, etc.— then the claim recites new matter. Applicant must limit the claim such that new matter is not encompassed.

Also, it was noted supra that it is unclear whether claim 37 is referring to a "non-lysine amino acid" that is the residue before or after alteration. Only the latter is supported by the disclosure.

Also, it was noted supra that it is unclear whether claim 53 is referring to the C-terminal amino acid residue before or after alteration. Unless this clearly claims the antibody based fusion protein after alteration, there is new matter.

Regarding prior art rejections of record, Applicant's amendment has argued a 102 (a) rejection based upon Gillies et al (WO 99/43713). It is noted that under the 103 rejection over Gillies et al in view of Chang et al, the examiner considered Gillies et al as anticipating some claims. The examiner does not consider Gillies et al as anticipating any instant claim; the change from P (posit. 446 of IgG1) to L (posit. 443 of IgG4), shown in Fig 2B of Gilles et al, is not a change to a more non-polar/hydrophobic amino acid.

Applicant is referred to US Pat. 6,646,113, col. 56 for a Table showing a listing of the common amino acids, arranged with the charged/most polar at the top and the less polar/hydrophobic at the bottom.

Claims 1-2, 4-8, 13-19, 24, 29, 34, 36-37, 46 and 48-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gillies et al in view of Chang et al (5,908,626 or 5,723,125).

Gillies et al show fusion proteins in which there is an N-terminal Ig H-chain (gamma 1 and gamma 4 exemplified) fused to a C-terminal IL-2 ("non-Ig protein"); see Example 1. These two segments are directly fused sans use of a linker. Chang et al teach that insertion of a gly-ser linker at the junction point of a fusion protein reduces immunogenicity of a fusion protein. Examiner has previously stated obviousness on the basis that one would have been motivated to insert the gly-ser linker of Chang et al into the junction point of the fusion proteins of Gillies et al in order to reduce immunogenicity. The examiner considers that insertion of the gly-ser linker would inherently increase the hydrophobic nature of the junction region of the fusion protein; note that gly and ser are more non-polar/hydrophobic than adjacent C-terminal G-K residues of IgG1 or adjacent L-G-K residues of IgG4 (Gillies et al, Fig 2B). In thus inserting a gly-ser linker, the examiner takes the position that one reasonably would have expected that the increased hydrophobicity introduced by the linker would increase the half-life; applicant's own disclosure provides extrinsic evidence.

The amended version of claim1 does not overcome the rejection of record, because the examiner considers that one cannot distinguish, in the final fusion product, what is added to the C-terminal of the Ig chain or the N-terminal of the non-Ig protein versus what is added as a linker. Claim 1 requires that there be "an amino acid alteration to a hydrophobic or non-polar amino acid within 10 amino acids of the N-terminus of the C-terminal non-Ig protein". The examiner considers that addition of G-G-G-S (4 right most residues of linker of Chang et al) constitutes the addition of non-polar/hydrophobic amino acid residues to the N-terminus of the IL-2 (the C-terminal non-Ig). The examiner sees nothing in the phrase "amino acid alteration" that rules out such N-terminal additions. The examiner also considers that what is being claimed

is the final fusion construct; one need not have any idea as to how it was arrived at; it is thus proper to interpret the 16-mer linker of Chang et al as being, instead, an 12-mer linker fused to an IL-2 that has had G-G-G-S added to its amino terminus to increase its hydrophobicity. Thus claims 1-2, 7-8, 24, 29 and 46 are anticipated. The IL-2 of Gillies et al is consistent with instant claims 5-6, 13-14 and 16. The alterations taught by Gillies et al (pgs 6-16) render their fusion protein as having less affinity for the receptors recited in claims 11-12. In addition to fusion to IL-2, Gilles et al teach fusion to TNF alpha, GM-CSF, CD4 and CTLA-4 (pg 3); thus all of dependent claims 13-19 are rejected.

The examiner takes claims 48-49 as being consistent with the fusion protein of Gillies et al in view of Chang et al. Note that the language "alteration to a hydrophobic or non-polar amino acid within 10 amino acids from the C-terminus of the Ig chain" is consistent with the addition of G residues (left most residues in the linker of Chang et al) to the Ig H-chain C-terminus. This change is also consistent with dependent claims 2, 7-8, 24, 29, 34, 46 and 50.

Dependent claim 4 is included because the addition of Gly (left most amino acid residue in the linker of Chang et al) to the C-terminal of the Ig segment is consistent with recitation of the broadest reasonable interpretation of an "alteration that changes the C-terminal amino acid". Further dependent claims 36-37 are included because the added Gly has a non-ionizable side chain and because it is not Lys.

Claims 51-52 are rejected because the addition of Gly (left most amino acid residue in the linker of Chang et al) to the C-terminal of the Ig segment is consistent with recitation of the broadest reasonable interpretation of "the Ig chain comprising an amino acid sequence that is non- natural within 10 amino acids from its C-terminus"; the examiner sees nothing in this

language that negates addition of a Gly to the C-terminal, since the addition results in a sequence that is "non-natural".

Applicant is referred to US Pat. 6,646,113, col. 56 for a Table showing a listing of the common amino acids, arranged with the charged/most polar at the top and the less polar/hydrophobic at the bottom.

Applicant's arguments filed 10/23/03 have been fully considered but they are not persuasive.

New prior art rejections based upon references of the disclosure statement filed on 11/6/03 follow:

Claims 1-2, 4-7, 11-14, 16, 24-25, 29, 34-37 and 46-52 are rejected under 35 U.S.C. 102(b) as being anticipated by Fell et al, J Immunol, 146, 2446-2452, 1991 (ref C43).

Fell et al show a fusion protein in which an N-terminal Fab (Ig portion) is fused to a C-terminal IL-2 (non-IG portion). Fig. 1 shows the fusion point junction and the amino acid changes introduced therein. These are changes from C to P and C to S in the C-terminal portion of the CH1/hindge domain of the human gamma 1 H-chain (see * marks in Fig. 1) and introduction of a 13-mer linker between the Ig and the IL-2 portions. The examiner sees these changes as increasing the overall hydrophobicity of junction area; while there are three charged residues of R introduced, all other residues introduced (P, S, G, V, A, L, M) are non-charged and are more non-polar/hydrophobic than the amino acid residues they replaced (C in the gamma 1 H-chain) or of other amino acid residues that remain near thereto (e.g. D, K and H in the gamma-1 H-chain). The examiner takes this increase in hydrophobicity as inherently leading to an increase in the circulating half-life of the altered fusion protein of Fell et al, compared to what it

would be without any of the alterations, or without the 13-mer linker. Applicant's own disclosure provides the extrinsic evidence that it is the increase in hydrophobicity that is crucial to increasing the circulating half-life.

The claims are of sufficient breadth that the examiner interprets these as encompassing the altered fusion protein of Fell et al. Claim 1 requires that there be "an amino acid alteration to a hydrophobic or non-polar amino acid within 10 amino acids of the N-terminus of the C-terminal non-Ig protein". The examiner considers that addition of A and M (2 right most residues of linker in Fig. 1) constitutes the addition of two non-polar/hydrophobic amino acid residues to the N-terminus of the IL-2 (the C-terminal non-Ig). The examiner sees nothing in the phrase "amino acid alteration" that rules out such N-terminal additions. The examiner also considers that what is being claimed is the final fusion construct; one need not have any idea as to how it was arrived at; it is thus proper to interpret the 13-mer linker of the reference as being, instead, an 11-mer linker fused to an IL-2 that has had A and M added to its amino terminus to increase its hydrophobicity. Thus claims 1-2, 7, 24, 29 and 47 are anticipated. The IL-2 in Fig. 1 of Fell et al is consistent with instant claims 5-6, 13-14 and 16. The fact that the Fab of Fell et al has no CH2 and CH3 domains renders their fusion protein as having less affinity than intact IgG1 for the receptors recited in claims 11-12.

The examiner takes claims 48-49 as being consistent with the fusion protein of Fell et al. Note the Ig chain in Fell et al is from the CH1 domain of the human gamma-1 H-chain; this is consistent with claims 48-49 and dependent claims 7 and 50. Note that the language "alteration to a hydrophobic or non-polar amino acid within 10 amino acids from the C-terminus of the Ig chain" is consistent with the C to P and C to S substitutions in the gamma-1 chain of Fell et al;

this change is also consistent with dependent claims 2, 25 and 34. Dependent claim 24 is rejected since Fell et al show a 13-mer linker.

Dependent claim 4 is included because the addition of Gly (left most amino acid residue in the linker of Fell et al) to the C-terminal of the Ig segment is consistent with recitation of the broadest reasonable interpretation of an "alteration that changes the C-terminal amino acid". Further dependent claims 36-37 are included because the added Gly has a non-ionizable side chain and because it is not Lys. Addition of Gly to the Ig terminus would also be consistent with instant claim 46.

Dependent claim 35 is included because a change from a Cys to a Ser (penultimate residue in the gamma –1 segment of Fell, Fig. 1) codon can involve a point mutation (G to C at 2nd residue of codon).

Claims 51-52 are rejected because the changes in the gamma-1 chain shown by Fell et al provide "an amino acid sequence that is non-natural within 10 amino acids from its C-terminus" and constitute "an alteration to a hydrophobic or non-polar amino acid".

Applicant is referred to US Pat. 6,646,113, col. 56 for a Table showing a listing of the common amino acids, arranged with the charged/most polar at the top and the less polar/hydrophobic at the bottom.

Claims 1-2, 4-8, 11-12, 24, 34, 36-37 and 46-52 are rejected under 35 U.S.C. 102(b) as being anticipated by Mann et al (WO 98/28427, ref B71).

Mann et al teach fusion proteins having an N-terminal Fc region fused to a C-terminal OB protein. The sequences disclosed and the proteins exemplified have these two segments directly fused; however, page 9, lines 7-23 indicate that there can be a linker between these two

segments; those with several ala residues, or with several gly residues, and especially those with a pro residue added thereto would be expected to introduce a high degree of hydrophobicity in the junction region. While the disclosure gives no experimental comparison of circulating half-lives of the fused proteins, with and without such a linker, one would expect that the increased hydrophobicity introduced by the linker would increase the half-life; applicant's own disclosure provides extrinsic evidence.

As in the rejection supra over Fell et al, the examiner considers that one cannot distinguish, in the final fusion product, what is added to the C-terminal of the Ig chain or the N-terminal of the non-Ig protein versus what is added as a linker. For example, suppose that one has a first fused protein with linker (b) of Mann et al (i.e. 4 ala residues); suppose also that one has a second fused protein with linker (c) of Mann et al (i.e. 5 ala residues): one could equally well consider this second fused protein to be one with ala added to the C-terminus of the Ig chain, plus a 4-mer linker of ala; also, one could equally well consider this second fused protein to be one with ala added to the N-terminus of the non-Ig, plus a 4-mer linker of ala. The latter of these interpretations is considered consistent with instant claims 1-2: the former interpretation is considered consistent with instant claims 48-49 and 51, as well as dependent claim 24 and 46-47.

Dependent claim 4 is included because the addition of Ala or Gly (left most amino acid residue in the linkers of Mann et al) to the C-terminal of the Ig segment is consistent with recitation of the broadest reasonable interpretation of an "alteration that changes the C-terminal amino acid". Further dependent claims 36-37 are included because an added Ala or Gly has a non-ionizable side chain and because it is not Lys.

The Fc segment of Mann et al can be from human IgG1—IgG4 (pg 7, lines 15+). This is consistent with instant dependent claims 7-8, 34, 50 and 52.

Regarding dependent claim(s) 11-12, note page 8, lines 23+

Regarding dependent claim(s) 5-6, Mann et al appear to use sequences that are of the mature form of the OB protein; note pages 10-11.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David A Saunders, PhD whose telephone number is 571-272-0849. The examiner can normally be reached on Mon-Thu from 8:00 to 5:30. The examiner can also be reached on alternate Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David A Saunders

DAVID SAUNDERS
PRIMARY EXAMINER
ART UNIT ~~182~~ 1644